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Placental transfer and fetal uptake of amino acids in the pregnant ewe

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Analysis of fetal carcass protein, from the calf (JACOBSEN et al. [16]) and rat (SOUTHGATE [34]), has shown that the **amino acids are the same,** and present in the **same proportions,** as in weanling and adult protein (WILLIAMS et al. [37]). This indicates that all the **amino acids are probably transferred across the placental barrier,** because it is known that the enzymes converting essential to non-essential amino acids are not always active in fetal liver until after birth (JAKUBOVIC [17], and GAULL et al. [8]). Experimental evidence for this transfer has been obtained in the guinea pig with the fetal placenta perfused 'in situ'; **each essential amino acid,** with the exception of threonine and tryptophan, and the majority of non-essential amino acids, **were shown to be transported from the maternal plasma, across the placental membrane against a concentration gradient** (YOUNG and HILL [37]).

It is a well known fact that the **free amino concentration in maternal plasma is low during gestation,** at a time when it might be expected to be maintained to ensure a fetal supply. The purpose of the present study was to observe the **influence of an increase in the concentration of the free amino acids in the maternal circulation upon transfer into the fetal plasma.** The plasma concentrations were raised, within physiological limits, by a single injection of a mixture of amino acids, given intravenously. Placental transfer rates of the three transport groups were compared, namely, the **straight chain** and **branched chain** amino acids and the **basic** amino acids (CHRISTENSEN [1]). **Fetal uptake** rate was also measured following a single injection of amino acids directly into the fetal circulation. Finally fetal and maternal **metabolic clearance rates (M. C. R.)** and **plasma half life ($t^1/_2$)** were compared to look for differences in metabolism between the young and adult animal. Some preliminary results have been published. (HOPKINS et al. [13, 14] and YOUNG [38]).

Curriculum vitae

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Holds post of Reader in Reproductive Physiology in Dept. Gynaecology, St. Thomas's Hospital Medical School, London. Investigator and teacher.
Present research concerned with growth, nutrition and metabolism of fetus. The influence of placental blood flow and of maternal: fetal plasma gradients of amino acids and glucose on placental transfer is being investigated in the guinea pig and sheep.
Participated in the development of the acid-sodium citrate glucose mixture for blood storage.

Methods

1.1 Experimental procedure

Seventeen Scottish Blackface ewes were studied at gestational ages between 135 and 145 days. They were kept in the animal house 3—5 days before the experiment, and fed on hay and cake. Two received 250 mg Proluton, 18 hours before operating. The average weight of the pregnant ewes in the flock was 72 kg.

The observations were made under **low spinal anaesthesia,** obtained with 1 ml 0.5% Nupercaine in 6% glucose. The ewe was placed on her back and the uterus exposed through a mid-line abdominal incision. The umbilical vessels were catheterised by COMLINE and SILVER's [2] modification of the method used by MESCHIA et al. [28]. The cord was located by palpation through a 2—3 inch incision in the artero-median surface of the uterine wall, and small branches of one umbilical vein and an artery were cannulated with No. 90 polyethylene tubing (1.27 mm outside diameter, 0.86 mm inside diameter) filled with heparin saline (30 IU/ml); the catheters were threaded 15 cm into the main umbilical vessels and tied in. After the uterine incision had been closed, a lateral uterine vein was cannulated through as mall tributary with No. 90 polythylene tubing, passed 30 cm down the main vessel. The abdominal well was closed. The maternal aorta was catheterised with No. 50 polyethylene tubing (0.96 mm outside diameter, 0.58 mm internal diameter) passed up the femoral artery, for the collection of blood and for arterial blood pressure measurement. Fetal blood pressure was measured from the umbilical artery, and acid base samples were taken from the umbilical vein.

1.2 Maternal uptake and maternal to fetal transfer of amino acids

A mixture of six amino acids, containing from 0.08—1.3 g of each dissolved in 50 ml 0.9% saline, and calculated to **raise the maternal plasma levels three to five fold,** was injected into the jugular vein; 10 ml blood samples were taken from the maternal uterine vein and aorta, and 4 ml samples were collected from the umbilical vessels simultaneously 2, 5, 10, 15, 30 and 60 minutes after the injection, and analysed for plasma free amino acids.

1.3 Fetal uptake of amino acids

A mixture of six amino acids, containing from 11 to 220 mg of each dissolved in 4—13 ml saline, was **injected into either the umbilical** vein **or the umbilical artery:** the injection catheter was well cleared with saline and blood sampling from both vessels made at the same time intervals as in the maternal to fetal transfer experiments just described.

1.4 Techniques

Arterial blood pressures were measured with Statham strain gauges (p23D) using Cardiac Recorders amplifiers and ultra violet recording. **Maternal arterial and fetal umbilical vein pH. PO_2 and PCO_2** were measured at 38°C on 1 ml samples using Astrup micro electrodes. **Haematocrite** measurements were made on the control and final blood samples sealed in capillary tubes and spun in a Hawsley centrifuge.

Free amino acids were measured in 1.5 ml maternal plasma, and 0.75 ml fetal plasma, after precipitation of the proteins with 5 ml saturated picric acid, and the addition of 0.5 μ moles norleucine internal standard, in 1 ml; the supernatant was stored at —10°C. Excess picrate was removed on a Dowex column, before separation of the amino acids by ion-exchange chromatography by a single column gradient elution technique (Technicon Instruments Co., Basingstoke, England). 22 amino acids were estimated: proline and tryptophan were not measured; glutamine and asparagine are partially hydrolysed by the method, the remainder being eluted with threonine and included in this value. The error was 5%.

2. Results

The mean blood **gas tensions and pH** (± S. D.) in the maternal artery and in the umbilical vein, at the beginning of the observations are shown in Tab. I together with the **haemotocrit** values. Small changes occurred in each during the experiment, but were not significant: the **pH and PO_2 fell** in each and the **PCO_2 remained constant;** the **maternal haematocrit rose and the fetal fell.** The mean maternal arterial pressure was 100 mm Hg (± S. D. 7 mmHg) and the umbilical arterial pressure 57 mmHg (± 12 mmHg).

Tab. I. Blood gas tensions, pH and haematocrite in the pregnant ewe and her fetus under spinal anaesthesia.

	Maternal artery		Fetal umbilical vein	
	Mean	±S. D.	Mean	±S. D.
pH	7.48	0.09	7.29	0.14
PO_2 mmHg	83.5	10.4	26.9	5.6
PCO_2 mmHg	31.9	4.3	40.2	7.9
Haematocrit	29.4	5.6	44.6	6.0
n	15		15	

Tab. II. A. Resting fetal: maternal free plasma amino acid concentration ratios.
B. Fetal plasma free amino acid changes following maternal loading. These are related both to the control fetal and maternal levels. The neutral branched chain amino acids are transferred most freely across the placental membrane. The amino acids are arranged in the order in which they are eluted from the chromatographic column.
● Neutral branched chain; ○ Basic amino acids.

	Umb. V. / Mat. Art.	% change, mean (±S. D.) in Umb. V. plasma conc^n.				Rise in Umb. V. as % Mat. Art. Conc^n. Mean.		Amino acid injected [g]	No. of observ^n.
		5 mins		15 mins		5 mins	15 mins		
Taurine	1.60								
Aspartate	5.41								
Threonine	4.70								
Serine	10.27								
Glutamate	1.56								
Citrulline	1.52	—15	15	—20	54	—24	—33	0.38	4
Glycine	1.80								
Alanine	2.96	36	17	32	54	20	17	0.76	4
-Aminobutyrate	11.31								
● Valine	3.23	115	102	100	60	193	168	0.48	5
Cystine	1.48								
Methionine	3.53	23	7	15	6	256	168	0.17	3
● Isoleucine	1.99	106	11	128	90	277	331	0.41	4
● Leucine	2.49	58	30	44	36	70	54	0.25	6
Tyrosine	4.16								
● Phenylalanine	4.23	48	16	59	29	194	237	0.37	4
○ Ornithine	1.81	14	36	3.3	14	37	9	0.21	5
○ Lysine	2.81	—5	20	—25	28	—7	—34	0.49	3
1-CH_3 histidine	3.07								
○ Histidine	2.12	0.4	17	—9	15	1	—21	0.43	4
3-CH_3 histidine	2.61								
○ Arginine	1.67	6	16	9	17	11	15	0.36	5

2.1 Maternal and fetal plasma free amino acid levels

Fig. 1 shows the mean (± S. E.) of the values for the maternal arterial and fetal umbilical vein plasmas. The aminogram has been arranged in order of magnitude of the maternal plasma levels. The fetal levels were all higher than the maternal and the **average fetal: maternal concentration ratios** across the placenta are found in Tab. II they range **from 1.5 to 11.3.**

2.2 Arterio-venous differences of the free plasma amino acids on the maternal and fetal side of the placenta

The mean of paired arterio-venous maternal and umbilical veinartery differences for the plasma amino acids are shown in Fig. 2; because of the large scatter of results the values are not significantly different from zero. The **maternal values are the larger** and demonstrate **uptake by the placenta and uterine muscle,** which is the greatest for serine and alanine. Most of the umbilical vein-artery differences show **uptake by the fetus:** the negative values for glutamate, citrulline, glycine and alanine, suggest uptake by the placenta from the fetal circulation.

2.3 Maternal to fetal transfer

The quantities of amino acid injected into the maternal jugular vein were chosen so that the free plasma levels were raised three to five fold. Fig. 3 shows the influence of this rise on the fetal plasma levels, and fetal uptake for leucine and for ornithine. The fetal umbilical vein levels were higher than the maternal arterial and the A—V differences for each amino acid on both sides of the placenta small. Leucine was trans-

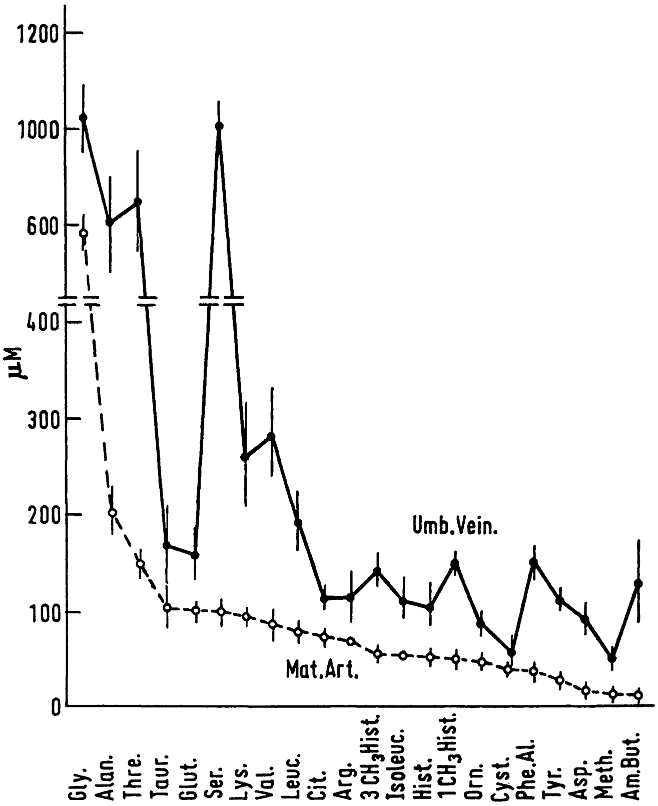

Fig. 1. Plasma aminograms for the maternal arterial and fetal umbilical vein blood; the free amino acids (mean ± S. E.) are arranged in the order of magnitude of their concentrations in the maternal plasma.
In maternal plasma 'n' = 13 for 17 of the 22 amino acids and was never less than 7. In fetal plasma 'n' = 12 for 15 of the amino acids studied and was never less than 9.

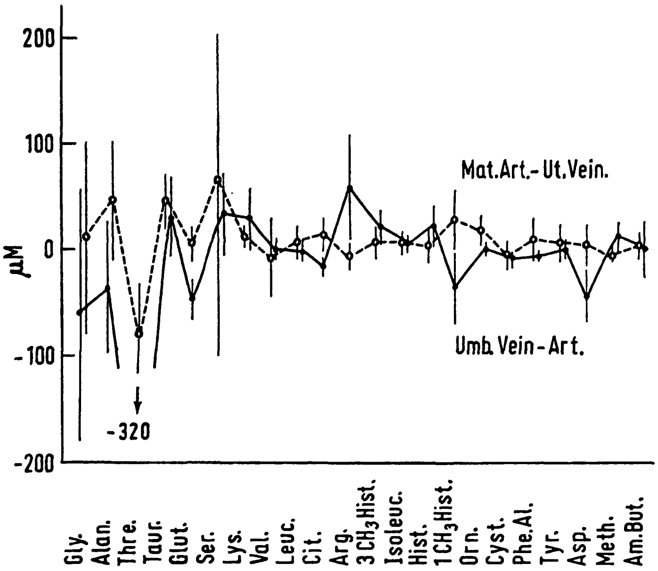

Fig. 2. Plasma free amino acid arterio-venous differences (mean ± S. E.) on the fetal and maternal sides of the placenta in the pregnant ewe. Seven paired observations were made and the mean values are not significantly different from zero.
For umbilical vein-artery differences 'n' = 7 for 13 of the 22 amino acids and was 3 for 2 of these. For the maternal artery-vein differences 'n' = 7 for 15 of the amino acids, and 4 on one occasion.

ferred readily across the membrane raising the fetal levels; the umbilical V—A differences, and therefore, fetal uptake was also increased. A raised level of ornithine in the maternal plasma influenced the level in the fetal blood only slightly.

Tab. II shows the results for all the plasma amino acids studied: the quantities injected into the maternal circulation are given together with the average percentage increase in the umbilical vein levels 5 and 15 mins following this injection. The **branched chain amino acids,** valine, isoleucine, leucine and phenylalanine all show the **largest increase in umbilical vein concentration** five minutes after the maternal injection, which is maintained after fifteen minutes:

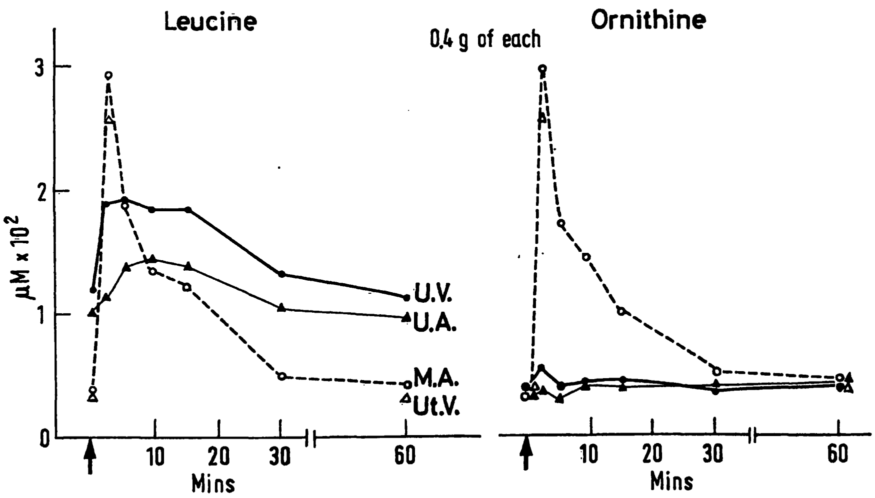

Fig. 3. Changes in the maternal and fetal plasma free leucine and ornithine concentrations following a single injection of 0.4 g of each into the maternal blood streams. The maternal A-V differences and umbilical V-A differences are small. Fetal plasma leucine levels are raised while those of ornithine only marginally so. The umbilical V-A differences for leucine is also increased indicating an increased fetal uptake.

the rise is 32—145% of the control value but the levels attained never reached the raised maternal values. The **straight chain neutral amino acids** alanine, together with citrulline, and the basic amino acid lysine, histidine, ornithine and arginine each **show a smaller rise** and some times a fall after five minutes; these changes were maintained for fifteen minutes. The transfer curves for taurine, aspartate, threonine and serine and glycine were irregular and the results are not presented. Cystine and glutamic acid, proline and tryptophan were not studied.

2.4 Plasma half life and metabolic clearance rate (M. C. R.)

Plasma half lives and metabolic clearance rates were studied using the excess decay curves following single intravenous injections of the amino acids in the maternal and fetal blood streams. The half life ($t_{1/2}$) was calculated in the conventional fashion from a line fitted to the first part of the exponential curve, plotted on semi-logarithmic paper, and extrapolated to zero; the plot was linear for 10—15 minutes and thereafter consisted of several slower rate constants. Metabolic clearance rate (M. C. R.) was calculated by dividing the quantity injected by the area under the excess decay curve during 60 mins and expressing the result in ml · min^{-1}kg^{-1} (GURPIDE [92]).

M. C. R. is defined as the ratio of the irrevisible removal rate of a metabolite from the blood stream, to its concentration in the peripheral blood.

The results are shown in Fig. 4. The maternal $t_{1/2}$ ranges from 7 to 4 mins for the different amino acids; the value is significantly shorter for the basic than for the neutral straight chain and branched chain amino acids. The fetal $t_{1/2}$ are **not significantly different** from the maternal values for any of the amino acids. The maternal M. C. R. was 10—14 ml min^{-1} kg^{-1} and **no significant differences** were observed between the groups; the two fetal values averaged 26 ml min^{-1} kg^{-1}.

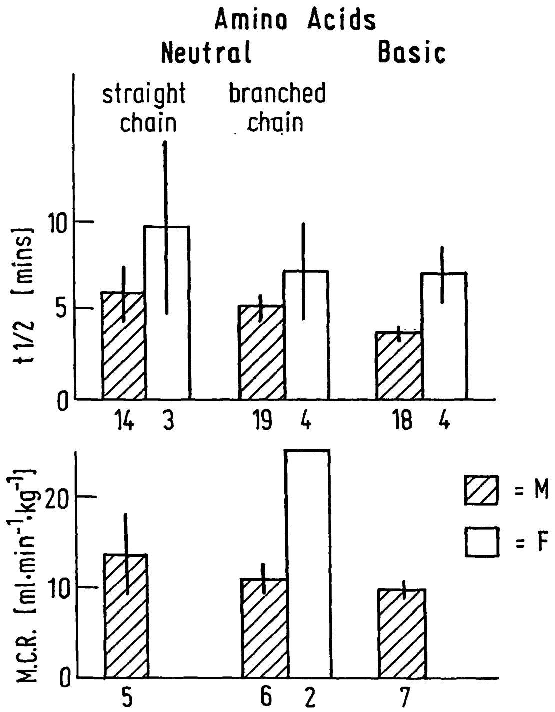

Fig. 4. Plasma half life ($t_{1/2}$ in minutes) and metabolic clearance rate (M. C. R. in ml · kg^{-1} min^{-1}) in the pregnant ewe and her fetus. (Mean ± S. E.) The number of observations are indicated under the histograms.
The maternal $t_{1/2}$ for the basic amino acids is significantly shorter ($p < 0.05$) than for the neutral straight and branched chain amino acids: the fetal values are not significantly different from the maternal.
No significant differences were found between the M. C. R. for the three groups of amino acids in the ewe.

3. Discussion

The maternal arterial blood **acid base characteristics** were similar to those found COMLINE and SILVER [2, 3] under nembutal anaesthesia and in chronic preparations; the fetal pH and PO_2 values were a little lower, suggesting some inpairment of the placental circulations due to the spinal anesthesia which was found by LUCAS et al. [24].

The **plasma amino acid** values in the pregnant ewe were **lower than in the non pregnant sheep** (LEIBHOLZ [20]) as might be expected from the fall in total α-amino nitrogen observed by CURET et al. [4] during gestation in the ewe. The **general pattern** and level of the amino acid concentrations in the maternal plasma were **similar to that found in the human subject** (YOUNG and PRENTON [40]) and in the guinea pig (HILL and YOUNG [12]); the high glycine is characteristic of other ruminants, while the branched chain amino acids, valine, isoleucine and leucine are low in comparison with the cow and the goat (VERBEKE and PEETERS [35], MEPHAM and LINZELL [26]). LEIBHOLZ's [21] finding of 1 and 3 methylhistine in the sheep plasma was confirmed for both mother and fetus.

The high free amino acids in the umbilical vein plasma confirmed the findings of HUGGETT and SLATER [15]) in the sheep; the **fetal: maternal ratios** for each individual amino acid were **higher than in the pregnant woman at term** but lower than those observed in the guinea pig. The fetal: maternal ratios are the highest for alanine, glycine and serine. **The differences between fetal and maternal plasma are mostly due to different amino acid metabolic equilbria on each side of the placental membrane;** in the guinea pig, with the fetal placenta perfused 'in situ', the amino acid pattern of the perfusate was different from that of the fetal plasma and resembled the composition of maternal plasma (YOUNG [38]). FELIG [7] has evidence that alanine is the main precursor for gluconeogenesis and the high levels of alanine in fetal plasma suggest that this funktion is not so active in the fetal lamb as in the ewe. The fetal: maternal ratio for cystine was one of the lowest, as was found in the human subject and in the guinea pig.

The **A—V differences** across the maternal side of the placenta were **larger than in the human subject.** The umbilical vein-artery differences were small on the fetal side of the placenta, as observed in the human subject at Caesarian section and, because the paired differences were not significant it was not possible to calculate fetal uptake from the values. Total α-amino nitrogen arterio-venous differences across either the maternal or fetal side of the placenta are 0.2 mM in the sheep (CURET et al. [4]) and goat SETNIKAR [32] so that an average individual amino acid A—V difference of only 10 μM would be expected. A—V plasma amino acid differences are generally small across muscle (LONDON et al. [23], POZEFSKY et al. [29]) and visceral organs (ELWYN et al. [6]); they are however, larger across the mammary gland and have been equated with protein synthesis rate by this organ in the goat. (MEPHAM and LINZELL [26].)

Increasing the maternal plasma level of the majority of the amino acids, particularly the basic amino acids and those belonging to the neutral straight chain, 'A' preferring group of CHRISTENSEN [1] has a relatively small influence on the fetal plasma levels. This observation together with the fact that the concentration falls during gestation suggests that the trophoblast secretes amino acids at a constant rate. The placental transfer of amino acids must, therefore, be primarily dependent upon the active process at the membrane together with the magnitude of the maternal boodl flow. This conclusion is strengthened by the findings, in the perfused guinea pig placenta, that amino acid transfer is independent of flow on the fetal side of the placenta, when this is varied within physiological limits; at very low flows, the placental secretion causes a marked rise in their concentrations in the umbilical vein plasma (REYNOLDS and YOUNG [31]). The faster transfer rates of the neutral branched chain amino acids, belonging to CHRISTENSEN's 'L' preferring group, is in accord with findings for the relative transfer rates of the amino acids across other multicellular membranes, and is probably due to their greater lipid solubility (REISER and CHRISTIANSEN [30]). Placental transport is, therefore, related to transport grouping rather than to essentiality of the amino acid; four of the eight essential amino acids belong to this 'L' preferring group.

The broad shape of the transfer curve in the fetal plasma must be due to the accumulation of the amino acid within the placenta and its subsequent release into the fetal blood stream which has been demonstrated using isotopes (HAYTER et al. [10]). The amino acid load given to the mother, 5—7 mg/kg was calculated to raise her plasma level within physiological limits; in previous studies of placental transport, by maternal loading with amino acid, much larger and unphysiological quantities, 50—200 mg/kg, have been given (KERR et al. [18], LINES et al. [22], DIERKS-VENTLING et al. [5], and WAPNIRE and DIERKS-VENTLING [36]). Inhibition of transport does not usually occur in 'in vitro' studies until concentrations exceed 1 mM (LARSON et al. [19], MATTHEWS et al. [25]). Such concentrations were not reached in the present investigations, but the reduction in fetal plasma citrulline, lysine and histidine levels, following a maternal injection, suggest that some inhibition may have occurred for these amino acids. CHRISTENSEN [1]) has also pointed out that two or more amino acids may have an additive influence and cause inhibition of transfer of another amino acid. This effect was not observed, for six amino acids were usually studied together and no changes occurred in the other plasma amino acid levels, in either the fetal or maternal plasma. The plasma half life of 4—7 mins observed for amino acids in the ewe is comparable with values obtained in other non-pregnant animals using radio-actively labelled amino acids (HENRIQUES [11]). These $t_{1/2}$ values represent K values of 18 for lysine and 11—13 for the straight and branched chain neutral amino acids: the volumes of distribution range from 158—182 ml · kg^{-1}. The fetal plasma half life is not different from that in the ewe, and fetal metabolic clearance rate is possibly higher than in the mother. Plasma clearance measurements are, however, crude and depend upon uptake and metabolism by a variety of tissues with different relative mass and blood flows and, probably, some different metabolic pathways in the mother and fetus. More detailed metabolic studies will be needed to demonstrate differences between both mother and fetus and between the transport groups in the intact animal.

Summary

1. The **pattern of the free plasma amino acids in the pregnant ewe and her fetus** at 135—145 days gestation are described. The **concentrations of all the amino acids,** both essential and non essential, **was highest in the fetal plasma** demonstrating different metabolic equilibria on either side of the placental membrane. Serine, alanine and glycine concentrations were particularily elevated.

2. Uterine arterio venous differences showed **uptake of amino acids by the placenta and uterus.** The umbilical vein artery differences were small but the **majority of the amino acids were taken up by the fetus.** Glutamate, citrulline, alanine and glycine were frequently higher in the umbilical artery than in the vein and taken up by the placenta.

3. Placental transfer rate for the three transport groups, the **straight and branched chain neutral,** and the **basic** amino acids, were compared after a **five fold increase in the maternal plasma level.** A rise in the neutral branched chain amino acids had the greatest influence on the fetal levels. The results suggested that **placental transfer was related to transport groups,** rather than to essentialness of the amino acid. Further, that a **constant maternal to fetal secretion** rate of **amino acids occurred** which was **relatively independent of the maternal plasma concentrations.**

4. The plasma clearance rate of the basic amino acids was faster than for both the neutral transport groups in the ewe. **Fetal plasma clearance rate did not differ from the maternal** and, therefore, provided **no information on any differences in metabolism between the two.**

Keywords: Amino acids, animal experiment, placenta.

Zusammenfassung

Diaplazentarer Transport und fetale Aufnahme von Aminosäuren beim schwangeren Schaf

1. Es wurde das **Aminosäuremuster der freien Plasmaaminosäuren bei schwangeren Schafen und deren Feten** nach 135—145 Tagen Tragzeit beschrieben. Die Konzentrationen aller Aminosäuren, sowohl der essentiellen als auch der nicht-essentiellen, waren **am höchsten im fetalen Plasma,** was einen unterschiedlichen metabolischen Gleichgewichtszustand auf beiden Seiten der Plazentarmembran anzeigt. Serin-, Alanin- und Glycinkonzentrationen waren besonders erhöht.

2. Arterio-venöse Unterschiede im Uterus beweisen eine **Aufnahme von Aminosäuren durch Plazenta und Uterus.** Die venös-arteriellen Differenzen in der Nabelschnur waren gering; **die meisten Aminosäuren waren durch den Feten aufgenommen.** Glutamat, Citrullin, Alanin und Glycin waren häufig höher in der Nabelarterie als in der Vene und durch die Plazenta aufgenommen.

3. Die **diaplazentare Transferrate** für die **drei Transportgruppen,** nämlich die **geradkettigen und verzweigten neutralen** und die **basischen** Aminosäuren, wurden verglichen nach einer 5fachen Erhöhung des mütterlichen Plasma-Spiegels. Eine Erhöhung der neutralen verzweigtkettigen Aminosäuren hatte den größten Einfluß auf die fetale Konzentration. Die Ergebnisse legen nahe, daß der **diaplazentare Transport eher korreliert ist mit der Transportgruppe als mit ihrer Eigenschaft als essentieller Aminosäure.** Außerdem ergibt sich, daß eine konstante **Sekretionsrate der Aminosäuren von der Mutter zum Feten** stattfindet, die relativ unabhängig ist von der mütterlichen Plasmakonzentration.

4. Die Plasma-Clearance der basischen Aminosäuren war schneller als bei beiden neutralen Transportgruppen beim Schaf. Die fetale Plasma-Clearance unterschied sich nicht von der mütterlichen und liefert somit **keinerlei Anhalte für Stoffwechselunterschiede** zwischen beiden.

Schlüsselwörter: Aminosäuren, Tierexperimente, Plazenta.

Résumé

Transfert placentaire et captation des acides aminés chez la brebis gestante

1. **Le taux des acides aminés libres dans le plasma de la brebis gestante et de leurs foetus,** entre 135 et 145 jours de gestation, sont décrits dans cet article. Les concentrations de tous les acides aminés, essentiels et non essentiels, sont **plus élevées dans le plasma foetal,** ce qui démontre **une différence d'équilibre métabolique de part et d'autre de la membrane placentaire.** Les concentrations en sérine, alanine et glycine sont particulièrement élevées.

2. Les différences entre les taux artériels et veineux utérins montrent une **captation des acides aminés par le placenta et l'utérus. Les différences de taux entre la veine et l'artère ombilicale sont petites,** mais la majorité des acides aminés sont captés par le foetus. Glutamate, citrulline, alanine et glycine sont souvent plus élevées dans l'artère que dans la veine ombilicale, ce qui signifie une captation au niveau du placenta.

3. Le taux de transfert placentaire pour les acides aminés neutres, droits ou ramifiés, et les acides aminés basiques sont comparés après que le taux plasmatique maternel soit augmenté cinq fois.

Une augmentation du taux des acides aminés à chaine neutre ramifiée influe particulièrement sur le taux foetal. Les résultats laissent penser que **le transfert placentaire est surtout influencé par le mode de transport, tandis que le caractère essentiel ou non essentiel des acides aminés a moins d'importance.** D'autre part, il semble permis de penser qu'un taux de sécrétion constant de la mère vers le foetus peut s'établir et que ce taux est relativement indépendant de la concentration plasmatique maternelle.

4. La clearance plasmatique des acides aminés basiques est plus rapide que celle des acides aminés neutres chez la brebis.
La clearance plasmatique foetale ne diffère aucunement de la clearance maternelle, et en conséquence ne procure aucune information sur les différences métaboliques éventuelles entre les deux.

Mots-clés: Acides aminés, expérimentation animale, placenta.

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